671

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office
HFI-35

60 8th Street, N.E.
Atlanta, Georgia 30309

July 28, 1997

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Marlin Miller
President/CEO
Arrow International, Inc.
2400 Bernville Road
Reading, Pennsylvania 19605

WARNING LETTER

Dear Mr. Miller:

An inspection of your firm located in Asheboro, North Carolina, was conducted on May 19-23, 1997. Our investigator found that you are manufacturing and distributing a variety of catheter products. These products are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The investigator documented several significant deviations from the Good Manufacturing Practice for Medical Devices (GMPs) as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 820. These deviations cause the devices you manufacture and distribute to be adulterated within the meaning of Section 501(h) of the Act.

You have failed to appropriately validate the sterilization equipment and process in use. You could not provide documented evidence which established a high degree of assurance that the sterilizers and the sterilization process in use are effective and could consistently produce a product meeting its predetermined sterility specifications and quality attributes. You have failed to appropriately validate the software for the computer controlled sterilizers.

The specifications for the software requirements for chambers [redacted] and [redacted] were not representative of the software currently in use. The software description document provided to the investigator was dated September 1993. This document failed to describe the intended functions of the computer software in terms of the inputs, processing, and outputs for each program element. There have been at least ten revisions made to the software between its installation in March 1995 and April 1996. There was no documentation available of any revisions made since April 1996. Neither Arrow nor the software manufacturer could provide information as to any changes made since April 1996. Although there have been numerous changes to the software,

the software requirements have not been updated or revised to reflect the current operating system. Prior to March 1997 these changes had not been the subject of any attempt to validate the software. The significance of each of these changes and the potential impact on the system had not been evaluated.

Sterilizer chambers [redacted] and [redacted] have been in use since March 1995 and April 1995 respectively. No software requirements testing has been completed on these computer controlled systems as installed. Although some testing was performed in March and April 1997 on these chambers, your firm has yet to complete its review of the data generated. The reason given for this failure was that Arrow was still working on the systems prior to initiating validation.

The software test plan which is currently in use to test the sterilizer software included no description of how test cases were developed or how thorough test coverage is to be achieved. There is no assurance that the software test plan currently being utilized is one which will provide complete test coverage. As the software requirements have not been updated since September 1993, assurance of complete test coverage can not be shown. The software test plan in use is not traceable to the current software specifications requirements for the system.

There is no documented correlation between the user requirements, software functional elements, and software verification activities to assure thorough test coverage. The verification activities in the test plan do not show traceability to established software requirements specifications to ensure that the specifications have been met.

The installation qualification performed on chambers [redacted] and [redacted] was also found to be deficient. You failed to demonstrate the ability of the systems to perform within their design specifications. The documentation available lacked a complete description of the sterilizers to include ancillary systems. The ability of the ancillary systems to produce the required quality of air, steam, water, and power was not assessed.

Your firm's attempt to demonstrate the equivalence of chambers [redacted] and [redacted] was also found to be inadequate. An equivalence study was performed to eliminate the process validation requirement for chamber [redacted] The study only compared the ability of the two cycles to provide similar temperatures and pressures within the cycle parameters. No physical comparison of the equipment and ancillary systems was available.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. At the close of the inspection, the Inspectional Observations (FDA 483) was issued to and discussed with Ernest L. Confer, Plant Manager. A copy of the FDA 483 is enclosed for your review. The specific violations noted in this letter and in the FDA 483 could be symptomatic of serious underlying problems in your firm's quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submission of devices to which the GMP deficiencies are reasonably related will be cleared until these violations have been corrected. Also, no request for Certificates For Products for Export will be approved until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory actions being initiated by the FDA without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within fifteen (15) days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

We have completed our review of the response to the FDA 483 submitted by Mr. Confer on May 30. We have continuing concerns with the response which will be addressed in a letter to be issued to Mr. Confer this week. FDA has previously brought the need to properly validate sterilizer software to the attention of Arrow. This was discussed in a Warning Letter issued to your firm in August 1994. Your response should be sent to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely yours,

for Roger E. Kline

Ballard H. Graham, Director
Atlanta District

cc: Ernest Confer, Plant Manager
Arrow International, Inc.
312 Commerce Place
Asheboro, NC 27203